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EDITORIAL COMMENT

Atrial Fibrillation*

The Ancient Conundrum Defies Simple Solution

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> ". . . Eli sat on his seat by the wayside watching; for his heart trembled . . ." Samuel I, 4:13

Atrial fibrillation (AF), affecting 2% to 4% of adults aged 60 years and older and more than 10% of patients older than 80 years (1), is heralded with the onset of dyspnea, chest discomfort, palpitations, or simply fatigue, as the Biblical judge, Eli, experienced (possibly the earliest description of AF). However, as many as one-third of patients may have asymptomatic or "silent" AF, which is more common in the elderly (2).

DOES SILENT AF PREDISPOSE ONE TO SILENT STROKE?

Computed tomographic imaging in 141 asymptomatic subjects with non-valvular AF revealed that 36 (26%) had a hypodense area consistent with a cerebral infarction (3). Silent stroke has significant ramifications even though it is by definition "asymptomatic." Elderly people with silent brain infarct on cerebral magnetic resonance imaging (MRI) have greater than double the risk of dementia and a steeper decline in global cognitive function (4).

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The current study by Bernhardt et al. (5) in this issue of the *Journal* reinforces the dangers of AF even with apparent adequate anticoagulation and rate control. They followed 128 patients with nonvalvular AF and dense spontaneous echo contrast (SEC) in the left atrial appendage (LAA) compared with 143 patients with faint SEC. During the subsequent 12 months, 2% had symptomatic cerebral embolism, 6% died as the result of their embolic event, and 15% had silent embolism. Those patients with a cerebroembolism, clinical or silent, had a significantly lower LAA emptying velocity and denser spontaneous echo contrast compared with patients without an event (similar to Stroke Prevention Atrial Fibrillation [SPAF] III findings) (6).

Atrial fibrillation is a hypercoagulable state with elevated fibrinogen, D-dimer, plasma C-reactive protein, soluble P-selectin, and von Willebrand factor. Stasis in the LAA can lead to fibrinogen-promoted red blood cell aggregation, forming dense SEC (7). The combination of stasis and hypercoagulable state may promote thrombus formation. Thus, by confirming the presence of low contractile velocity and "dense SEC" in the LAA, transesophageal echo may be able to identify patients at highest risk for subsequent clinical and/or silent cerebrovascular events despite adequate anticoagulation.

WHY DIDN'T WARFARIN PREVENT THE CEREBROVASCULAR EVENTS?

The current guideline for warfarin anticoagulation in patients with sustained paroxysmal AF at high risk of stroke is a target international normalized ratio (INR) of 2.5, range of 2 to 3.0 (8). In the current study, patients with nonvalvular AF and dense spontaneous echo contrast had an increased risk of cerebral embolism or death despite continued oral anticoagulation, with a mean INR of 2.3 ± 0.3 (5). Confounding compulsive supervision, patients may dip below the magic number INR of 2.0. In a meta-analysis of 21 studies involving patients with nonvalvular AF on warfarin, 26.0% of patients were below the therapeutic target INR of 2 to 3, with a 2.1% incidence of clinically apparent cardioembolic events (9). Thus, warfarin may not be absolutely effective in preventing large, clinical emboli nor emboli to clinically silent, compensated, or "noneloquent" regions of the brain.

CAN WE IMPROVE ON WARFARIN PROPHYLAXIS?

A recent randomized, multicenter trial from Spain of 1,209 patients examined the use of anticoagulants (acenocoumarol), antiplatelets (triflusal), or combination therapy in intermediate- and high-risk patients with AF (10). The median INRs in the intermediate- and high-risk groups were 1.93 and 2.17, respectively. The combined therapy of anticoagulant and antiplatelet medication resulted in a lower incidence of vascular death, nonfatal stroke, and systemic embolism than either alone, with no difference in the incidence of severe bleeding. Despite the greater potential risk of bleeding, the Seventh American Chest Physicians Conference on Antithrombotic and Thrombolytic Therapy recommended adding aspirin in doses up to 100 mg/day to oral anticoagulation (target INR 2 to 3) in patients with AF and atherosclerosis to prevent ischemic coronary events (8). Thus, randomized trials with medications available in the U.S. are warranted to determine whether a combination of anticoagulant and antithrombotic agents could prevent even silent events at an acceptable risk, particularly in the elderly.

IS AF RATE CONTROL AN ACCEPTABLE GOAL?

Two recent large studies (Rate Control vs. Electical Cardioversion for Persistent Atrial Fibrillation [RACE] and

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Atrial Fibrillation Follow-up Investigation of Rhythm Management [AFFIRM]) that compared rate control versus rhythm control in AF concluded that rhythm control offered no survival advantage over rate control (11,12). However, a follow-up of the AFFIRM study according to the actual treatment patients received, not by intention to treat as reported in the initial article, demonstrated that the presence of sinus rhythm was associated with a lower risk of death (13). Additionally, Hsu et al. (14) demonstrated that patients with congestive heart failure in sinus rhythm after AF ablation had significant improvement in left ventricular function, exercise capacity, and quality of life at 12 months. Thus, an effective strategy for maintaining sinus rhythm with minimal adverse effects might improve function and survival in patients with AF and eliminate embolic complications.

CAN SINUS RHYTHM BE MAINTAINED?

A multivariate analysis of the AFFIRM study reported that of 2,033 patients who received 3,030 exposures to antiarrhythmic drugs, the risk of an adverse arrhythmic event was reasonably low (15). However, <50% of patients on an antiarrhythmic regimen will remain in sinus rhythm at the end of one year, mandating continued chronic anticoagulation.

Ablation of AF foci is one of the non-pharmacologic therapies for eradicating AF. The surgical Maze procedure has a >90% success rate of maintaining sinus rhythm (16). Electrophysiologists have adapted the Corridor and Maze procedures with pulmonary vein isolation procedures with similar success rates. However, complications of catheter ablation include stroke, cardiac perforation, cardiac tamponade, atrial-ventricular heart block, and pulmonary vein stenosis and thrombosis.

Both patient-activated and automatic atrial antitachycardic pacing therapies have been used to painlessly treat atrial arrhythmias. The "pill-in-the-pocket" treatment of paroxysmal AF was recently described using either flecainide or propafenone and was shown to restore sinus rhythm in 94% of patients treated within 36 ± 93 min (17). However, episodes of "silent AF" would not be self-treated, exposing the subject to the risk of cardioembolism.

Thus, the current study emphasizes the dangers of AF even when the rate is well controlled and the patient is seemingly adequately anticoagulated. With the aging of the population, more patients will present with clinical or silent atrial AF. Strategies designed for AF rate control, even with admirable attempts at maintaining adequate INRs, may expose patients to risks of major embolic events and their sequelae and/or silent cerebral emboli, with subsequent development of cognitive impairment that otherwise is attributable to aging alone. Aggressive strategies providing better pharmacologic antiembolic protection while maintaining sinus rhythm with pharmacologic, percutaneous ablation, or implantable defibrillators appear preferable to AF rate control.

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